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USSR WORK ON HEMORRHAGIC NEPHROSO-NEPHRITIS

[Comment: The following report consists of excerpts from, and summaries of, parts of the text of Gemorragicheskiy Nefroso-Nefrit (Hemorrhagic Nephroso-Nephritis) by A. A. Smorodintsev, V. G. Chudakov, and A. V. Churilov. This book aims to establish a connection between the Far Eastern hemorrhagic nephroso-nephritis investigated by USSR workers, the so-called epidemic hemorrhagic fever described by Japanese workers, and the various hemorrhagic fevers (Omsk, Crimean, Bukovina, Uzbekistan, etc.) occurring on the territory of the USSR in regions other than the Far East. While references have been made repeatedly to the possibility that the Far Eastern hemorrhagic nephroso-nephritis and the USSR hemorrhagic fevers are closely related, no detailed and complete USSR study of the subject was available in the US prior to receipt of copies of the book by Smorodintsev et al. On the basis of a discussion of Japanese work, the authors of the book arrive at the conclusion that the clinical aspects and pathology of the epidemic hemorrhagic fever described by the Japanese and the hemorrhagic nephroso-nephritis investigated by themselves in the USSR coincide completely (cf. p 14).

As far as the etiology and epidemiology of these two diseases are concerned, the similarity is less clear. According to the data cited in the book, it appears on the basis of the Japanese work that mice and Gamasidae mites which infest these mice function as a reservoir of the disease. The presence of the virus in the mites has been established (p 14). On the other hand, the USSR investigators, while assuming that many species of small rodents may participate in the transmission of the virus, have established with certainty only that Mikhno's Eastern vole (Microtus michnoi Kastschenko) functions as a transmitter and reservoir of the disease (pp 23-25 and 31). The mechanism of the transmission of the disease from infected rodents to humans was not clarified and the presence of the virus in ectoparasites of Eastern voles could not be established in the USSR work reviewed in the book (p 31).

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Possibly the reference in the Japanese publication discussed by the Russian authors (p 14) should have been to members of the mouse family, to which Eastern voles also belong, rather than to "mice."

In addition to outlining USSR research on hemorrhagic nephroso-nephritis done during the period 1932-1947, the book is also intended to serve as a manual for physicians treating this disease. In tables for differential diagnosis (pp 108-17), the differences between hemorrhagic nephroso-nephritis and a number of individual diseases with which it may be confused (influenza, croup pneumonia, typhus, jaundice-free leptospirosis, acute nephritis, perforation of the stomach or duodenum, Japanese mosquito-born encephalitis, tick encephalitis, Crimean hemorrhagic fever, Omsk hemorrhagic fever, and Uzbekistan hemorrhagic fever) are listed.

In selecting material from the book for inclusion in this report, emphasis has been placed on epidemiology and etiology rather than diagnostics and pathology. The table of contents of Gemorragicheskiy Nefroso-Nefrit is appended.]

General Background of Work on Hemorrhagic Nephroso-Nephritis

Among infectious diseases which are not very well known to medicine a prominent place is occupied by the group of virus-caused hemorrhagic fevers which are transmitted to human beings by blood-sucking ticks and mites.

Soviet scientists established the existence of characteristic hemorrhagic diseases which are encountered in an extensive territory covering the central and southern regions of the Soviet Union from the Far East to the Western Ukraine.

During the period 1940-1949 the etiological aspects, epidemiology, and clinical aspects of hemorrhagic nephroso-nephritis and of hemorrhagic fevers occurring in the Crimea, Omsk area, and Uzbekistan were uncovered.

Specific traits in the biology of the causative factors and transmitters of these diseases are responsible for differences in the epidemiology and clinical aspects of the diseases caused by these causative factors. However, there is a definite resemblance between the individual diseases that is determined by the biological characteristics which the causative factors have in common. These causative factors belong to a new group of viruses which have a selective affinity for blood vessels. In other words, they can be designated as hemotropic viruses.

The transmissive nature of all virus-caused hemorrhagic diseases that have been stu[illegible]d hitherto explains the similarities in their epidemiology. The common characteristic of their pathogenesis is a resemblance of the clinical aspects in which phenomena of a hemorrhagic diathesis predominate.

The first disease of this group that attracted the attention of Soviet physicians is the so-called hemorrhagic nephroso-nephritis which was discovered originally in the Far East. Wild rodents and their ectoparasites were found to form a natural reservoir of this disease.

In human beings infection with this disease is accompanied by fever, phenomena of hemorrhagic diathesis, an acute toxic condition, renal insufficiency, and characteristic changes in the blood and urine. Examination of the sections of organs discloses very specific changes which are typical for this disease, particularly changes in the kidneys. Incidences of the disease occur primarily during the period between April and November. They take the form of infections of whole groups or of individual cases of infection. The disease affects men

and women of various age groups and in rare cases also children. The population of sparsely settled areas which have a grass cover or are covered by shrubbery and are located on marshy ground or in the vicinity of rivers and lakes is chiefly affected.

Hemorrhagic nephroso-nephritis as an individual disease was recognized in 1935-1939 for the first time by physicians active in the Far East, i.e., A. V. Churilov, I. A. Miller, S. P. Irlin, and N. S. Isayev. The clinical aspects, pathology, and laboratory diagnostics of this disease were described for the first time in 1936-1939 by A. V. Churilov, L. S. Leybin, and M. I. Dunayevskiy.

On the basis of observations carried out on a great number of patients, A. V. Churilov clearly differentiated hemorrhagic nephroso-nephritis from other diseases. In his work (1941) the basic data on the characteristic cyclic manifestations of this disease are reported. On the basis of these data and also of systematic investigations carried out by G. M. Tsygankov, Sh. I. Ratner, L. I. Kazbintsev, D. M. Ayzenshteyn, and others, three principal periods are distinguished in the course of hemorrhagic nephroso-nephritis.

During the first period, corresponding to the first to 2d day of the disease, there are symptoms of a toxic condition, i.e., an increase of the temperature to 39-40°C, a strong shivering and chills, an acute headache, pain over the whole body, and sometimes vomiting. The face, the upper part of the chest, and the conjunctiva of the eyelids show a strong hyperemia. Bleeding from the nose is already often observed in this period. As far as the blood is concerned, there is leukopenia corresponding to 2,000-4,000 and accompanied by an increase in the number of rod neutrophils, sometimes by a reduction in the number of eosinophils, and by an appearance of Tuerck's cells and neutrophil myelocytes.

Changes in the urine generally do not occur, although occasionally traces of protein are present.

During the second period comprising the 3d to 7th day of the disease (on the 7th day the fever ceases) the patient is plagued by pain in the region of the waist and of the abdomen. The vomiting increases and there are hiccoughs. Particularly characteristic is the appearance of a fine petechial rash in the region of the upper thorax and under the arms, as well as of hemorrhages from the nose and in the stomach and intestines. The patients exhibit a typical putrid odor from the mouth and suffer from thirst. Oliguria develops and more seldom anuria sets in. On the 5th to 7th day of the disease, the quantity of protein in the urine reaches 1-3% or more. Erythrocytes are occasionally present in the urine and in the precipitate there are accumulations of characteristic cells which have a circular or oval shape and are vacuolized. Some cells have a nucleus resembling a bubble (these are modified renal epythelial cells). Elongated cylyndrical formations of a dense consistency and of what appears to be a fibrinoid nature are also found. In the blood the quantity of leukocytes is increased to 20,000-60,000. On the 4th to 5th day there are among them 1-10% of freshly formed neutrophils and neutrophil myelocytes, also 4-20% of Tuerck's cells.

After the temperature has dropped, on about the 5th to 7th day, the disease does not terminate, but enters the third period, which is the most painful for the patient. An acute local injury of the kidneys is typical for this period. The patient suffers severely from pains in the region of the waist, vomiting (he often vomits blood), hiccoughs, insomnia, and thirst. Oliguria of anuria continues. Profuse hemorrhages persist and the patient has no appetite. In the urine the quantity of protein and erythrocytes drops sharply, but fibrin cylinders are invariably present. The average duration of this period is 3-4 days.

The headache gradually diminishes, vomiting becomes less frequent, and oliguria is replaced by polyuria. A pronounced general debility, apathy, and irritability remain. Some authors refer to a fourth period, i.e., the period of recovery, which has a duration of 5-6 weeks. Throughout the duration of the disease, the blood pressure does not rise. During the second and particularly during the third period, there is an acute bradycardia. Edemas are not observed. During the disease, the patients lose 8-20 kg of weight.

The lethality in hemorrhagic nephroso-nephritis reaches 3 to 5%. Until 1939, a considerable number of cases of this disease was diagnosed incorrectly as toxic influenza, food poisoning, leptospirosis, meningitis, meningoencephalitis, perforation of the stomach or dnodennm, appendicitis, etc.

The correct diagnosis of the disease was subsequently aided by the application of laboratory methods of diagnosis which had been developed as a result of the systematic investigation by M. I. Dunayevskiy in 1939-1940, who discovered characteristic changes in the blood and urine which are typical for hemorrhagic nephroso-nephritis.

Work done by L. S. Leybin, A. G. Kestner, and V. G. Chudakov has clarified some problems of the pathogenesis and pathology of this disease.

The most significant factor in the pathogenesis of hemorrhagic nephroso-nephritis is formed by afflictions of the vascular and nervous systems, particularly as far as small blood vessels and the capillaries are concerned. The resulting changes in the blood vessels are accompanied by hemorrhages and a release into the tissues of a liquid rich in proteins. These changes are most pronounced in the kidneys, a phenomenon which is apparently connected with the elimination of the virus by the kidneys.

When sections of the kidneys are examined, the unusual appearance of the kidneys attracts attention. In addition to general hemorrhagic changes the dark cherry-red pyramids, which are saturated with blood, are prominent against the background of the pale, gray-yellow cortex matter. When the kidney is sectioned, blood flows profusely from the surface of the pyramids.

Until 1938, the etiology and epidemiology of the disease remained unknown. Beginning with 1938, active participation in the study of problems pertaining to hemorrhagic nephroso-nephritis was taken by expeditions of the Health Commissariat USSR and of the All-Union Institute of Experimental Medicine (A. A. Smorodintsev, I. I. Rogozin, S. I. Tarasov, and V. I. Terskikh) as well as by local physicians (V. D. Neustroyev, V. A. Eskin, I. L. Myrovannyy, A. V. Churilov, K. G. Vasil'yev, and others).

Investigations carried out in 1938-1939 by the group under A. A. Smorodintsev's direction demonstrated that the occurrence of hemorrhagic nephroso-nephritis is not connected with the infections with leptospira, aerobic or anaerobic bacteria, or rickettsiae. At the same time attempts to infect laboratory animals (guinea pigs, white mice, rabbits, white rats and monkeys) with the blood or urine derived from patients suffering from nephroso-nephritis and taken during the fever period of the disease remained unsuccessful. For that reason doubts arose in regard to the infectious nature of the disease. Some investigators began to regard the disease as acute scurvy brought about by a lack of vitamin C and culminating in a hemorrhagic diathesis.

An important stage in the study of the etiology of hemorrhagic nephroso-nephritis was formed by the work carried out by the Division of Viruses, All-Union Institute of Experimental Medicine (A. A. Smorodintsev et al.). This work was carried out in 1940 and published in 1944. The work in question convincingly demonstrated the infectious nature of the disease. It was established that the pathogenic agent appears in the blood and in the urine of patients

during the first 6 days of the disease and subsequently disappears. This phenomenon is apparently related to the accumulation in the blood of substances which neutralize the active pathogenic factor, because the serum of convalescents neutralizes the infectious factors of the blood of patients taken in the acute stage of the disease.

In view of the fact that the pathogenic factor passes through bacterial filters, we classified it as belonging to the new group of hemotropic viruses.

The virus of hemorrhagic nephroso-nephritis was found to be pathogenic to some rodents (the Eastern vole and others), among which the circulation of the virus is maintained by ectoparasites which may also transmit the infection to humans.

At present there are reasons to believe that hemorrhagic nephroso-nephritis is encountered not only in the Far East (in Manchuria and Northern Korea) but also in the European part of the USSR.

As has already been indicated above, hemorrhagic nephroso-nephritis, as far as its clinical, etiological and epidemiological aspects are concerned, exhibits some similarities with the hemorrhagic fevers that occur in the Crimea, Omsk area, Uzbekistan, Bukovina, and other localities and have been discovered during recent years. For that reason, we shall characterize briefly these new virus diseases.

The so-called Crimean and Omsk hemorrhagic fevers are the diseases of this group which have been studied most thoroughly (by M. P. Chumakov and his collaborators). Typical for these diseases are afflictions of the vascular and nervous systems and a frequent development of a hemorrhagic syndrome.

The principal results of the comprehensive study of the Omsk and Crimean hemorrhagic fevers that has been carried out is summarized by M. P. Chumakov, N. A. Zeytlenok, and I. S. Glazunov in an article entitled "The Investigation of Virus Neuroinfections and Hemorrhagic Fevers" which has been published in Sovremennyye Voprosy Meditsinskoy Nauki (Contemporary Problems of Medical Science), Academy of Medical Sciences USSR, 1951.

According to A. A. Kolachev, A. F. Bilibin, and R. M. Akhrem-Akhremovich, the clinical syndrome of these diseases is expressed in the following symptoms: hyperemia of the face and selera enanthema and hyperemia of the pharynx, fever continuing from 4 to 9 days, continuous changes in the blood (leukopenia, nuclear shift to the left, neutrophilia followed by lymphocytosis, thrombocytopenia, and prothrombinopenia). A hemorrhagic syndrome (bleeding of the gums, bleeding from the nose, etc.) is observed in the majority of patients and is accompanied by disturbances of the nervous system.

The clinical syndrome of Omsk hemorrhagic fever shows some differences from the syndrome of Crimean hemorrhagic fever.

In Omsk hemorrhagic fever, 25% of the patients develop a second wave of fever and 33% of the patients get pneumonia, while these phenomena are not observed in Crimean hemorrhagic fever.

On the other hand, a hemorrhagic rash and intestinal hemorrhages are very common in Crimean hemorrhagic fever, while these symptoms are absent in Omsk fever.

The pathomorphological syndrome of these diseases is characterized by a predominant affliction of the vascular and nervous systems (i.e., Robinzon, I. S. Novitskiy).

There are destruction and swelling of small blood vessels of various integuments and internal organs. As a result of this, a sharp increase in the permeability of the blood vessels develops and there are serous edema and manifestations of hemorrhagic diathesis.

On the part of the central nervous system, the following phenomena are typical: destruction of individual nerve cells and glia, formation of perivascular infiltrates from lymphoid elements around modified vessels of the cerebrum, and necrosis and proliferation of the glia cells.

In A. F. Bilibin's opinion, one must distinguish the following stages in the development of Omsk hemorrhagic fever:

1. An early and predominant affliction by the virus of the endothelia of blood vessels and of the suprarenals

2. Virusemia

3. Action of the virus on the organs of blood formation

4. A hemorrhagic diathesis

5. Disturbances in the water and protein metabolism, and

6. Inflammatory-toxic processes in parenchymatous organs (the liver, lungs, cardiovascular system, etc.)

The causative factors of the Crimean hemorrhagic fever and the Omsk hemorrhagic fever, i.e., the filterable viruses, can be regularly detected in the blood of feverish paints during the first days of the disease and in the bodies of the ticks which transmit the infection (M. P. Chumakov, et al). As far as their immunological and antigenic properties are concerned, the viruses of Omsk hemorrhagic fever and of the Crimea hemorrhagic fever can be easily differentiated from each other and from the causative factors of hemorrhagic nephroso-nephritis pappataci fever, Q-fever, and other rickettsioses. Each of the two hemorrhagic fevers mentioned is distinct with regard to its etiology.

White mice, monkeys, guinea pigs, cats, and voles are highly susceptible to the virus of Omsk hemorrhagic fever. This virus has neurotropic properties and propagates readily in the brains of white mice and in chicken embryos. Monkeys and mice which have been infected by introducing the virus into the brain develop meningoencephalitis. After prolonged passages through mice, the virus of Omsk hemorrhagic fever may acquire a high virulence and bring about an infection of the workers at the laboratory which as far as the clinical aspects of the disease are concerned, resemble completely Omsk hemorrhagic fever. In the blood of persons who have recovered, specific neutralizing and complement-fixing antibodies are found. Human beings and experimental animals that have recovered from the disease develop lasting immunity.

As distinguished from the virus of Omsk hemorrhagic fever, the virus of Crimean hemorrhagic fever could not be adapted to laboratory animals: it merely produces in them a sympton-free form of an experimental infection. When the virus of Crimean hemorrhagic fever was administered to mental patients for the purpose of pyrogenic therapy, these patients developed a fever which was quite typical as far as its clinical aspects were concerned and had a benignant course.

From the epidemiological standpoint, both the Crimean and the Omsk hemorrhagic fevers are characterized by a seasonal occurrence (the outbreaks take place in the spring and summer), occurrence of the disease in definite rural regions among persons who work, or temporarily live in the steppe, and a complete lack of contagiousness from person to person.

A decisive point in the investigation of the epidemiology of Crimean hemorrhagic fever and Omsk hemorrhagic fever was the detection of the mechanism of human infection. This mechanism depends on the participation of ticks which function as transmitters.

It was established that the tick Hyalomma marginatum Koch functions as the transmitter of Crimean hemorrhagic fever and that the tick Dermacentor pictus Herm. transmits the Omsk hemorrhagic fever. The participation of these transmitters in the infection of human beings was proven by regular presence of specific viruses in hungry adult ticks and nympha collected in the Crimea and in the Omsk oblast. The Dermacentor pictus ticks transmit the causative factor of Omsk fever in the process of metamorphosis and transovarially to their progeny. They transmit the disease to susceptible animals by biting them. The infection of narrow-headed voles [Microtus (Stenocranius) gregalis Pallas] with the virus of Omsk hemorrhagic fever proceeds in this manner. Fourteen days after infection, the virus can be detected in the blood, brain, and spleen of these animals. The search of animals which function as virus carriers under natural conditions was unsuccessful, which emphasizes the principal role of the Dermacentor pictus ticks not only as transmitters of Omsk fever, but also as a constant reservoir of this causative factor in nature. Various species of wild animals which are susceptible to infection with the virus are a supplementary factor in the dissemination of this virus in nature among ticks. These animals function as a source of infection to ticks only at an early age, i.e., during the short period of the development of an acute infection which arises after the first contact with infected ticks.

Human beings and animals which have been subjected to attacks by infected ticks often develop a symptomless infection. This is shown by the frequent occurrence of specific antibodies in human beings who never had a clinically discernible form of the disease and also the occurrence of such antibodies in wild and domestic animals investigated in the vicinity of the reservoirs of the infection.

After the virus of Omsk hemorrhagic fever had been isolated in 1947 at the laboratory directed by M. P. Chumakov, a method of active immunization against this disease was developed. A killed formalin vaccine was prepared from the brains of infected mice. In experiments with mice, administration of this vaccine conferred an immunity of considerable strength against large doses of the virus. In 1948, the effectiveness of this preparation was tested on 7,000 human beings who could come in touch with transmitters of the Omsk hemorrhagic fever. The persons who had been inoculated did not catch the disease. In this manner the possibility was created of curtailing sharply or even eliminating entirely this disease by the method of specific immunization.

For the treatment of persons infected with Crimean hemorrhagic fever, specific serum therapy is used successfully. In this method of therapy 20-40 milliliters of the serum of convalescents is injected repeatedly into the muscles. Penicillin proved effective in the treatment of complications which accompany the infection. Penicillin is administered during 3-4 days for this purpose. To counteract hemorrhagic phenomena, calcium chloride, ascorbic acid, vitamin K, glucose, and insulin are used.

The reactions of neutralization and complement fixation carried out on the serum of patients are best suited for laboratory diagnosis. The reaction of complement fixation is positive beginning with the 7th to 8th day of the

disease and remains positive during the first few months after recovery. The reaction of neutralization (in Omsk hemorrhagic fever) appears later, but persists for no less than 3 years. For that reason, it is particularly valuable for the retrospective diagnosis of this disease. Virological diagnosis which is based on the isolation of the virus from the organism of infected animals yields reliable results only in cases of infection with the Omsk fever. In Omsk fever, white mice can always be infected with the blood of patients taken during the first few days of the disease.

In the rural areas of Uzbekistan sporadic cases of the so-called Uzbekistan hemorrhagic fever have been recorded. The etiology of this disease has been studied by N. I. Khodukin and his collaborators.

As far as its clinical, pathological, and epidemological characteristics are concerned, the so-called Uzbekistan hemorrhagic fever most closely resembles Crimean hemorrhagic fever. As in Crimean hemorrhagic fever, hemorrhagic manifestations (bleeding from the nose, intestine, and uterus; hemorrhagic rashes) predominate. However, Uzbekistan hemorrhagic fever is distinguished by its acute character, which can be ascribed to the more serious disturbances of circulation and distrophic changes in all internal organs that occur in this disease.

The lethality in Uzbekistan hemorrhagic fever (30%) is higher than that in Crimean hemorrhagic fever (3%). As distinguished from the latter, intrahospital contagion has occurred in Uzbekistan and Turkmenian hemorrhagic fevers. The Uzbekistan fever is not accompanied by pneumonias, while 30% of the patients with Omsk hemorrhagic fever develop pneumonia.

The pathological changes in Uzbekistan hemorrhagic fever are expressed in afflictions of the walls of blood vessels and consequent development of a hemorrhagic diathesis. There are also extensive necrotic modifications in heart muscles and the kidneys. In G. N. Terekhov's opinion, which are in agreement with Yu. S. Sergeyeva's data in regard to hemorrhagic nephroso-nephritis and I. I. Robinzon's data in regard to the Crimean fever, the fundamental background of the pathogenesis of Uzbekistan hemorrhagic fever consists in a primary affliction of the ganglia of the vegetative nervous system. This affliction results in secondary trophic changes of the vascular walls which are very thoroughgoing, and also changes in the heart muscle, the kidney epithalium, and the liver epithalium.

A filterable virus is a causative factor of Uzbekistan hemorrhagic fever. This virus, similarly to the causative factors of hemorrhagic nephroso-nephritis and of Crimean hemorrhagic fever, cannot be readily adapted to laboratory animals. However, mice, cats, guinea pigs, and voles are susceptible to it. It has been possible to induce a benign form of the disease by the experimental infection in rabbits suboccipitally with the blood of patients taken during the first days of the disease. On the 6th to 12th day after infection, there is a brief increase in the temperature of the rabbits. The virus can be passed from rabbit to rabbit for a long time. It could be cultured on chicken embryos and stored for a long time in an active state at low temperatures.

Epidemiologically Uzbekistan hemorrhagic fever is also very similar to Crimean hemorrhagic fever. The disease has a rigidly seasonal character (cases occur in the spring and summer only). The maximum incidence of the disease occurs in June and July. As distinguished from hemorrhagic nephroso-nephritis and Omsk hemorrhagic fever, there is no rise of the incidence of Uzbekistan fever in the fall. Sporadic cases of the infection predominate; the infection of whole families is rare. Persons engaged in agricultural work are predominantly affected.

The infection of human beings takes place as a result of attacks by Hyalomma anatolicum ticks. The participation of Hyalomma detritum and Rhipicephalus turanicus ticks in the transmission of the disease is also possible. The possibility exists that the virus may be preserved temporarily in supplementary reservoirs formed by cattle and horses.

In Uzbekistan hemorrhagic fever, just as in the Crimean hemorrhagic fever, prophylaxis should consist in the control of ticks, which form the main reservoir of the virus. The picking of ticks from farm animals should not be carried out with bare hands, but by means of pincers and should be followed by destruction of the ticks by putting them into a fire or placing them in kerosene. As far as the danger of attacks by ticks during the sojourn on pastures, fields, etc., is concerned, personal prophylaxis is essential.

This prophylaxis should consist in the inspection of the body and the clothing after work, wearing of overalls, extermination of the grass and other small plants at the places where one spends the night, and treatment of these plants with hexachlorocyclohexane and DDT.

Less thoroughly investigated have been the etiology and epidemiology of a number of other diseases which are related to hemorrhagic nephroso-nephritis and occur in various areas of the USSR (Bukovina, Tadzhikstan, and other regions).

In 1940 the Japanese investigator Kitano described a disease which he called epidemic hemorrhagic fever (febris or purpura hemorrhagica epidemica), which in its clinicoepidemiological characteristics resembles hemorrhagic nephroso-nephritis very much. The existence of foci of this disease has been established by him in various regions of northeastern Manchuria, predominantly in low places. Incidences of the disease occur most frequently during the summer (May-June) and fall (October-November). Both Japanese military personnel and the civilian population were affected by the disease. Contact of human beings with rodents (field mice, voles, rats, and mice) plays a role in the infection with the disease. The greatest number of incidences occurs among persons who sleep on the naked earth; people who slept on covers did not catch the disease. One cannot become infected with the disease from sick persons. Those infected suddenly develop a fever, bradycardia, hyperemia of the face and of the conjunctiva, and phenomena of toxicosis and of a hemorrhagic diathesis. The hemorrhages have a petechial character and occur predominantly under the arms and on the mucous membranes of the cheeks and of the nasopharynx. In acute forms of the disease there are gastric hemorrhages, vomiting of blood, pronounced general toxic symptoms, headache, pain in the waist, vomiting, hiccoughs, thirst, loss of sleep, and vertigo.

As far as the blood is concerned, the initial leukopenia is followed in acute cases of leukocytosis and then by a return to normal after a drop in the temperature. A nuclear shift to the left is observed.

The protein in the urine reaches a level of 50%; there is a large quantity of fibrin and erythrocytes are often present. The lethality in this disease is 15%. When the kidneys have been sectioned, one observes swelling and an increase in the weight of the kidneys. The cortex has an opaque appearance and a gray-yellow color. The medulla is dark red and contrasts sharply with the cortex.

Histological examination shows that the lumen of the canules is filled with fibrin-like matter and that there are necrosis of the cells, edema of the interstitial tissues accompanied by cell infiltration, extension of the blood vessels, and hemorrhages.

Thus, the clinical aspects and pathomorphology of the hemorrhagic fever described by the Japanese investigators coincide completely with the syndrome of hemorrhagic nephroso-nephritis.

The causative factor of the hemorrhagic fever is a filterable virus. This virus stands freezing and drying very well.

On the basis of Japanese work, it is assumed that the virus penetrates into the body of human beings when the excrements of mites are rubbed into the skin. These mites are parasites of rodents rather than of human beings, because no bites inflicted by the mites have been observed on human beings. The rodents have a latent form of the infection. The Japanese investigators succeeded in producing an infection in monkeys (species not indicated) by infecting them with a suspension prepared from 200 triturated mites infected from rodents. The disease can be transmitted from infected monkeys to healthy monkeys and the latter then develop a disease which is analagous to that observed in epidemic hemorrhagic fever of humans. It is considered that horses are susceptible to infection with the virus of epidemic hemorrhagic fever, because they develop an increase of temperature after being infected with the virus. Gamasidae mites infesting small wild rodents function as transmitters of the virus.

In 1944 a booklet was published entitled Etiologia i Klinika Gemorragicheskogo Nefroso-Nefrita (The Etiology and Clinical Aspects of Hemorrhagic Nephroso-Nephritis). This booklet describes the work done by expeditions of the People's Commissariat of Public Health, USSR, and the All-Union Institute of Experimental Medicine. This work, which was carried out in 1938-40, proved the infectious nature of hemorrhagic nephroso-nephritis and the similarity of its causative factor to an ultravirus (A. A. Smorodintsev, et al.). In the present monograph an account is given of the contemporary data pertaining to the etiology, epidemiology, clinical aspects, and pathology of hemorrhagic nephroso-nephritis.

M. I. Dunayevskiy participated in the compilation of the present monograph. He outlined the basic data in changes which occur in the blood and urine in hemorrhagic nephroso-nephritis (pp 3-14).

Etiology

Investigations carried out on wild rodents which inhabit the Far East proved that Mikhno's Eastern voles are susceptible to hemorrhagic nephroso-nephritis. As distinguished from the disease in humans, hemorrhagic changes in voles take place in the spleen rather than in the kidneys.

The experimental infection was also produced in cats.

It has been established by A. A. Smorodintsev that the virus of hemorrhagic nephroso-nephritis can be cultured on chicken embryos (pp 15-24).

Epidemiology

A systematic investigation of the epidemiology of hemorrhagic nephroso-nephritis has been conducted since 1938. The principal data on the epidemiology of this infection have been collected and systematized by I. L. Murovannyy, K. G. Vasil'yev, I. I. Rogozhin, M. D. Kashirin, and A. A. Smorodintsev.

It has been established that the epidemiology of hemorrhagic nephroso-nephritis is characterized by a number of specific traits which indicate the connection of the human infection with the presence in the region of a natural reservoir of the virus formed by infected rodents.

The disease is most frequently found among animals of well-defined regions when these regions possess a definite set of natural characteristics. Most often the regions affected are banks of rivers, river valleys, lakes surrounded by extensive fields and overgrown with a high and dense grass, low, sparse shrubbery, small trees that are widely spaced, or small groves. More seldom the region is an open marshy area or a section of the tayga [northern woods]. Incidences of the disease in mountain tayga regions located 400-500 meters above the sea-level are extremely rare.

Most conducive to the spread of this disease is a warm climate with an average temperature of 15-17° C from May to September. The disease affects most frequently persons who reside in sparsely populated regions. Only individual cases of the disease are observed in densely populated areas and these cases do not comprise more than 1-3% of the total.

Until recently hemorrhagic nephroso-nephritis was considered a specific disease of the territories of the Far East disposed in the Amur Basin, in the Khankay Lowlands, in the river valleys of the southern maritime region, Manchuria, and Korea. However, this view is not entirely correct, because the occurrence of analogous infections in the European part of the USSR has been established.

Characteristic of regions affected by hemorrhagic nephroso-nephritis is the large population of rodents of the mouse type (different species of voles, field mice, and the karako rat). Of particular significance from the epidemiological standpoint is the Eastern vole. In localities where the Eastern vole does not occur, no incidences of hemorrhagic nephroso-nephritis have been registered. It is not impossible that the infection is transmitted by other species of small wild rodents as well (field mice, forest mice, domestic rats, and mice). A considerable accumulation of these rodents can be found near the places where human beings spend the night, because these rodents are attracted by kitchen garbage. The size of the population of Eastern voles fluctuates strongly from year to year; in years where there is a high incidence of hemorrhagic nephroso-nephritis, a considerable increase in the number of Eastern voles is observed, while in years when the disease does not occur frequently, the number of eastern voles is small because they have died out as a result of floods or for other reasons.

Among the rodents that have been tested, the Eastern vole was found to be the only species that is susceptible to the causative factor of hemorrhagic nephroso-nephritis. Eastern voles which have been infected with the blood of sick persons develop a nonlethal infection with pronounced hemorrhagic symptoms.

The fact that we were able to isolate from the blood of the Eastern vole the virus of hemorrhagic nephroso-nephritis in 1947 confirms the role of this rodent as a virus carrier forming a natural reservoir (pp 24-35).

Therapy

In view of the fact that the etiology of hemorrhagic nephroso-nephritis is still in the course of investigation, a specific etiotropic therapy of this disease is not available as yet. The experience acquired in the treatment of patients who suffer from hemorrhagic nephroso-nephritis with the serum of recovered persons is rather meager: we do not yet have convincing data which indicate that this method of treatment is effective. Furthermore, the majority of patients are admitted to hospitals at a rather late stage, when the application of the serum cannot be expected to have the desired effect. For that reason the therapy of hemorrhagic nephroso-nephritis, although based in part on the knowledge of certain pathogenic mechanisms of the disease is still basically symptomatic. Therapeutic measures which are applied aim to counteract intoxication of the organism, chloridopenia, and the increased permeability of the vascular walls. These measures

have the purpose of lowering the excessive irritation of the central nervous system by pathological products of metabolism and thus of contributing to a normalization of the nervous reflex activity directed towards restoration of the disturbed equilibrium brought about by the toxic state of the body.

In order to increase the stability of the blood vessels and reduce hemorrhages, calcium chloride in the form of a 2% solution is administered intravenously in a quantity of 150-200 milliliters every 2d day.

It is recommended to administer simultaneously with calcium chloride large doses of ascorbic acid (10 milliliters of a 5% solution intravenously 2 times per day). To counteract the chloridopenia, the dehydration of the organism, and oliguria, one must use a physiological solution of sodium chloride extensively.

Subcutaneous administration of a sodium chloride solution to patients with hemorrhagic nephroso-nephritis, who have a tendency to develop hemorrhages, often result in the development of large bruises and hematomas. For that reason we administer medicinal solutions (a physiological solution of sodium chloride and a 5% solution of glucose) by means of a drop enema in a quantity of 3-4 liters per day. We inject a hypertonic solution of sodium chloride (50-100 milliliters of a 10% solution) intravenously whenever there is a sharp drop of the level of chlorides in the blood as a result of constant vomiting. Experience has shown that extensive application of chlorides always exerts a beneficial effect on the patients, particularly those of them who develop hemorrhagic forms of the disease. It has been found that introduction of a large quantity of sodium chloride and of calcium chloride results in a rapid lowering of the residual nitrogen of the blood. Elimination of azotemia sometimes requires urgent measures: administration of chlorides is often more effective from this standpoint than bloodletting.

Administration of glucose is also indicated: a 40% solution of glucose should be administered intravenously or, still better, a 3-5% solution subcutaneously or in the form of a drop enema. The glucose exerts a beneficial effect on the patients, acting as a nutrient and as a detoxifying substance. However, we prefer chlorides to glucose in the treatment of the hemorrhagic forms of the disease and use glucose in moderate doses only, because large doses of glucose apparently aggravate the course of these forms of hemorrhagic nephroso-nephritis unless a sufficient quantity of chlorides is also administered.

Administration of sodium chloride and of glucose requires constant control of the content of chlorides and sugar in the blood.

When the activity of the heart weakens, one gives camphor, caffeine, cordiamine [nikethamide], strophanthin, etc.

The application of the customary measures for combating vomiting (i.e., administration of chloroform water or of peppermint drops, swallowing of pieces of ice, drinking of a 1% solution of common salt and of sodium bicarbonate) is sometimes effective. In view of the fact that administration of drugs perorally in the form of powders and drops almost always induces vomiting, it is necessary to administer the drugs parenterally or in the form of enemas.

Various drugs (urotropin, salicylates, sulfanilamides, and penicillin) have been tentatively used in the therapy of hemorrhagic nephroso-nephritis, but without any success.

A. V. Vishnevskiy's lumbar novocain block, which has been tried at one time, has been found inadvisable, being dangerous because of the high sensitivity of the matter of the kidneys to trauma. Furthermore, the novocain block alleviated the pains in the waist for a short time only. Lately one often uses "omnopon" [pantopon] or morphine for alleviating the pains in the waist and in the abdominal region.

The diet of the patients must consist chiefly of dairy products and vegetables, although there is no necessity of eliminating meat entirely. The patients often refuse meat as well as sweetened dishes and prefer sour food. They eat with great appetite buttermilk, sour cream, kefir, and vinaigrettes made of fresh vegetables.

The foods should be salted according to the patient's taste: there is no reason to restrict the consumption of salt, because the patients often require salt.

The patients should be given food in small quantities and fed persistently even when there is frequent vomiting, because a part of the food still enters the intestinal tract notwithstanding the vomiting and is assimilated there.

The success of the treatment depends to a major extent on the care given the patients and the skill of the medical personnel.

The treatment of patients who have complications (parotitis, otitis, thrombophlebitis, or pneumonia) is considerably facilitated by the use of sulphonamides and penicillin. Although these drugs do not have any effect whatsoever on the causative factor of the disease, complications of a suppurative or inflammatory character are successfully treated by them.

Much more difficult is the therapy of the most serious complication in hemorrhagic nephroso-nephritis, namely a spontaneous rupture of the cortical matter of the kidneys. The removal of the damaged kidney, which has been suggested by some authors, is difficult to carry out because of the complex diagnosis and of the heavy trauma inflicted by the surgical operation on a patient who has an acute disease and a tendency to develop hemorrhages. Furthermore, the ruptures of the kidneys are often bilateral. The only measure which can be recommended at this stage is prevention of the occurrence of the complication. Prevention can be achieved by early hospitalization of the patients and adequate care during transportation. Patients having hemorrhagic nephroso-nephritis should not be transported in shaky vehicles or over bad roads. They stand transportation by plane well. In examining the patients one must avoid rough palpation in the region of the kidneys and sharp knocking in the region of the waist to test for Pasternatskiy's sympton (pp 118-121).

Table of Contents of Gemorragicheskiy Nefroso-Nefrit

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